Defying age: myth or reality?

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In this issue of *Haematologica*, Kawamura and others from Japan report on donor selection for allogeneic hematopoietic cell transplants in adults with hematologic malignancies.[1] They observed superior survival after transplantation of grafts from HLA-matched unrelated donors aged <50 years compared to matched siblings in patients aged ≥50 years. Compared to matched sibling transplantation, in patients aged ≥50 years, a survival advantage was not observed with older HLA-matched unrelated donors. In younger patients, survival did not differ after transplantation of grafts from HLA-matched unrelated donors or matched siblings. This report concluded with a donor selection algorithm based on the age of the patient. For patients aged <50 years, a matched sibling remains the donor of choice followed, in descending order, by: (i) an HLA-matched unrelated donor regardless of age, (ii) a 1-HLA locus mismatched related or unrelated donor or umbilical cord blood and (iii) a ≥2-HLA loci mismatched related donor. On the other hand, for older patients, an HLA-matched unrelated donor aged <50 years is the donor of choice followed, in descending order, by: (i) a matched sibling, (ii) an HLA-matched unrelated donor aged ≥50 years or a younger 1-HLA locus mismatched unrelated donor, (iii) a 1-HLA locus mismatched related or 1-HLA locus mismatched older unrelated donor or umbilical cord blood and (iv) a ≥2-HLA loci mismatched related donor.

Worldwide an increasing proportion of people are over the age of 65 years and in Japan they account for approximately 29% of the population making it important to address the needs of this growing population. Selection of unrelated donors for hematopoietic cell transplantation has evolved such that HLA-matching at the HLA-C locus and allele-level HLA-matching including for selecting umbilical cord blood units (after ensuring a minimum total nucleated cell dose per kilogram patient body weight)[2,3] have contributed to better survival after unrelated donor transplantation. An earlier report from the United States showed that for every 10-year increment in donor age, there is a 5.5% increase in the hazard ratio for overall mortality.[4] The World Marrow Donor Association (WMDA; *www.wmda.org*), an international body established in 1994, provides a global platform to improve access to hematopoietic cell transplantation. The WMDA's standards recommend unrelated donors must be aged 18-60 years with the option for unrelated donor registries to determine lower and upper donor ages with regard to registration and donation for their respective registries. In Japan, unrelated donors may join the registry aged 18 years and donate, beginning at 20 years, up to their 55th birthday.

How can the findings of Kawamura *et al*. inform changes with respect to the upper age limit for unrelated adult donors for donation, and donor selection applying evidenced-based data towards a revised donor selection algorithm?

First, based on the findings of Kawamura *et al*. should the upper age limit for donation be lowered to a donor's 50th birthday? Their report suggests that in Japan the median age at transplantation is the sixth decade. The report does not provide information on the demographics of the Japanese donor registry or the median age of donors selected through the registry. Nevertheless, consideration of revising existing guidelines for the donor registry will be influenced by real-world donor selection practice in Japan and available HLA haplotypes in the Japanese donor registry. Retaining donors with uncommon HLA haplotypes through their 55th birthday expands the donor pool whereas retaining donors with common HLA haplotypes beyond their 50th birthday is unlikely to be beneficial considering the potential benefit of selecting younger donors, other prognostic factors being equal.

Second, although the donor selection algorithm proposed by Kawamura *et al*. is evidenced-based, the worldwide applicability of some of its recommendations may be limited. There is agreement that younger adult unrelated and mismatched related donors improve survival.[5,6] Consequently, the practice of selecting a young HLA-matched unrelated donor instead of an older matched sibling may be acceptable worldwide. With the inclusion of high-dose post-transplant cyclophosphamide to the transplant regimen, survival has improved after transplantation of grafts

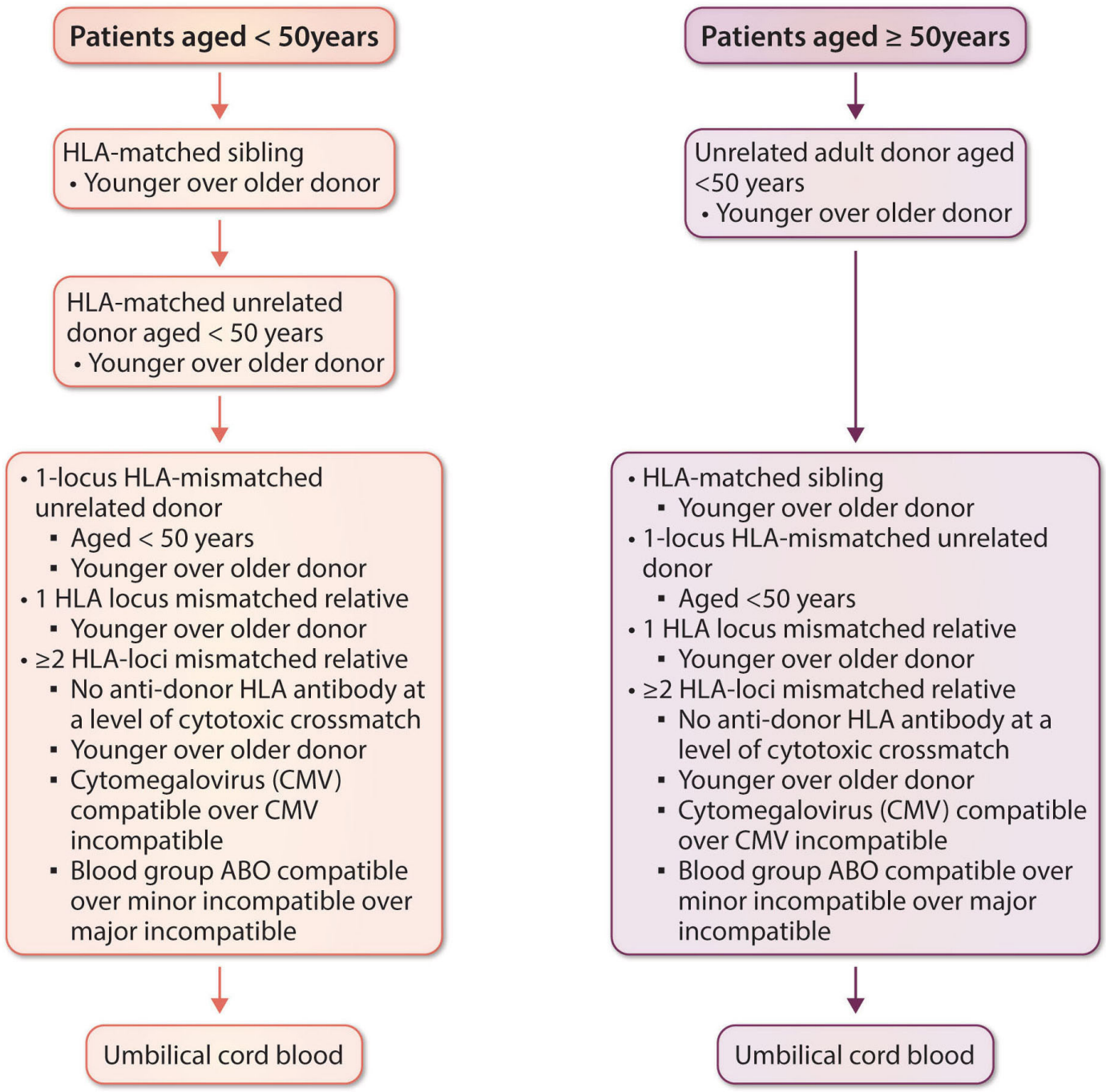

Figure 1. A simplified donor selection algorithm.

from ≥2-HLA loci mismatched related and 1-HLA locus mismatched unrelated donor transplantations to an extent that transplant outcomes are comparable to those after matched sibling transplants.[7,8] The use of umbilical cord blood as a graft has decreased substantially in recent years to an extent that these grafts now account for approximately only 1% of allogeneic transplants.[9] Ready availability of banked umbilical cord blood units was an advantage in past years when transplantation was needed urgently. However, with enhancements to donor search strategies offered through the unrelated donor registries the likelihood of identifying a fully matched unrelated donor (matched at the allele-level at HLA-A, -B, -C, -DRB1) is more readily apparent and offers an opportunity to proceed directly to an alternative donor without a prolonged search for a matched unrelated donor and without significant survival differences across the donor types although the 2-year survival ranged between 60% to 70%.[10]

What have we learned? The findings of Kawamura *et al.* and others have shown that selecting a young donor when available offers a survival advantage and must be incorporated into clinical practice. Most transplant centers would still choose an HLA-matched related or HLA-matched unrelated donor as their first choice. The choice of an alternative donor (i.e., HLA-mismatched related or unrelated donor or umbilical cord blood) will depend on a center's experience and opportunities to enroll patients into clinical trials testing novel strategies aimed at improving one or more transplant outcomes. More studies comparing alternative donor types are needed to advance knowledge as most patients nowadays are likely to have a choice of donors other than a matched sibling. In this context, a simplified donor selection algorithm is proposed for consideration with an understanding that this will be revised as future studies yield more knowledge regarding alternative donor selection (Figure 1). While the majority of allogeneic transplants are for hematologic malignancies and most data available have been gained from studying

such malignancies, there is a need to study donor selection for non-malignant hematologic diseases.

Disclosures

No conflicts of interest to disclose.

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